IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Atty. Docket: WALLACH=20

In re Application of:	)	Art Unit: 1647
	)	
David WALLACH et al	)	Examiner: D. Romeo
	)	
Appln. No.: 08/981,559	)	Washington, D.C.
Filed: April 13, 1998	)	March 12, 2002
For: TNF MODULATION	)	

BRIEF ON APPEAL

Honorable Commissioner for Patents
Washington, D.C. 20231

Sir:

Submitted herewith is applicant's Brief on Appeal in triplicate.

The present appeal is taken from the action of the examiner in rejecting claims 29 and 36 for at least the second time. The full text of claims 29 and 36 under appeal appears in Appendix A attached hereto.

REAL PARTY IN INTEREST

The present application is owned by Yeda Research and Development Co. Ltd., which is the research and development arm of the Weizmann Institute of Science in Rehovot, Israel. The exclusive licensee of the present invention is Inter-Lab Limited, an Israeli company of Ness-Ziona, Israel. Inter-Lab

Limited is a subsidiary of InterPharm Laboratories Limited, an Israeli company of Ness-Ziona, Israel, which is a subsidiary of Ares Serono N.V., whose parent company, Ares Serono S.A., is a holding company under which there are many subsidiaries worldwide.

RELATED APPEALS AND INTERFERENCES

Appellant is aware of no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

STATUS OF CLAIMS

Claims 29 and 36 presently appear in this case. Claims 29 and 36 are under final rejection. Claims 1-28 and 30-35 have been cancelled without prejudice toward the continuation of prosecution thereof in divisional applications.

STATUS OF AMENDMENTS

The most recent rejection in this case was a non-final rejection of July 12, 2001. No amendments to the claims have been filed subsequent to that date.

SUMMARY OF THE INVENTION

Tumor necrosis factor (TNF) is a cytokine that plays a central role in the induction of inflammation (page 1, lines 11-

12[1]). It has many effects on cells, some of which are beneficial to the organism, such as in destroying tumor cells, and some of which are deleterious, such as in contributing to septic shock (see page 2, lines 8-25). Thus, there is a long felt need to modulate the cellular response to TNF, such as to inhibit the TNF when its effects are deleterious or to enhance the effects of the TNF when such is desirable (see page 2, lines 26-29).

TNF molecules are initially produced in the form of a 26 kDa transmembrane protein. These transmembrane proteins may remain on the surface of the cells that produce them, or they may be proteolytically processed in order to yield soluble 17 kDa TNF molecules (see page 1, lines 16-20).

Both the cell surface and soluble forms of TNF can trigger effects characteristic of this cytokine in target cells by binding to the same two species of TNF receptors, the p55 TNF-R and p75 TNF-R, although there is some difference in action between the soluble form of TNF and the cell surface form (see the paragraph bridging pages 1 and 2 of the present specification).

The present invention is based on the discovery that the intracellular domain of the cell surface TNF molecules have phosphorylated residues (see page 5, lines 18-20). The present inventors state that the phosphorylation of the intracellular

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[1] All page and line citations in this section are to the present specification.

domain of the 26 kDa TNF molecule may be involved in the regulation of expression or proteolytic processing of cell surface TNF, in the modulation of TNF bioactivity, or in the intracellular signaling process mediated by the cell surface TNF molecules (see page 6, lines 3-6). Thus, the discovery of the phosphorylation of the intracellular domain of the cell surface TNF molecule represents the first disclosure of the possibility of controlling the cell surface form of TNF by control of the region in the intracellular domain of this form of TNF which is subject to phosphorylation (page 6, lines 7-10). The finding of phosphorylation of the intracellular domain of the cell surface bound form of TNF provides a basis for isolating agents and for pinpointing agents that can modulate the shedding of TNF, can modulate the activity of TNF by intracellular signaling induced by the intracellular domain of TNF, or can modulate the bioactivity TNF via conformational interactions mediated by the intracellular domain (see page 14, lines 1-7).

More specifically, the present invention is directed to a method for identifying and producing a molecule which causes modulation of the phosphorylation of the intracellular domain of the 26 kDa TNF. This method is accomplished by screening molecules by testing each molecule to determine if the molecule causes modulation of the phosphorylation of the intracellular domain of the 26 kDa TNF by increasing or decreasing the extent of such phosphorylation (see page 5, lines 3-6; and page 6, lines 7-10, for

example, as well as page 6, line 31 to page 7, line 3). Any molecule which is determined to cause such modulation is then produced in substantially isolated and purified form (see for example page 27, lines 5-11 and 25-27).

Preferably, each molecule is screened for binding to the intracellular domain of the 16 kDa TNF, and then tested to determine if any such molecule found to bind the intracellular domain modulates the phosphorylation of the intracellular domain of the 26 kDa TNF (see for example page 38, lines 1-15).

THE PRIOR ART

The rejection of July 12, 2001, contains no rejections over the prior art. Thus, there is no prior art which requires discussion in the present Brief.

THE REJECTIONS

In the rejection of July 12, 2001, claim 29 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, the Examiner stating:

> Claim 29 provides for the production of a molecule, but the claim does not set forth any steps involved in the production it is unclear what method/process applicant is intending to encompass [sic]. A claim is indefinite where it merely recites a process without any active, positive steps delimiting how this process is actually practiced.

Claims 29 and 36 have been rejected under 35 U.S.C. 101 on the ground that the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. The Examiner stated:

> The claims are drawn to or encompasses [sic] a method of screening for compounds that bind the intracellular domain of 26 kDa TNF and/or modulate the phosphorylation thereof. The specification teaches phosphorylation of the serine residues of the intracellular domain of 26 kDa TNF. However, the biological significance of this phosphorylation is unknown. In the absence of a knowledge of the biological significance of the phosphorylation process there is no apparent specific and substantial asserted utility or a well established utility for either the screening process or production of the compounds identified by the screening process. Further experimentation is necessary to attribute a utility to the claimed screening process. Evidence warranting further study is not equivalent to evidence showing the type of utility required by 35 U.S.C. 101. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966) (noting that in context of the utility requirement "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

Claims 29 and 36 were also rejected under 35 U.S.C. 112, first paragraph, on the ground that since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the 35 U.S.C. 101 rejection, one skilled in the art would not know how to use the claimed invention.

Claims 29 and 36 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, the Examiner stating:

> The claims are directed to "producing" a molecule. However, the specification does not describe the production of any and all molecules with the desired characteristics. At best it might be obvious to the skilled artisan that it would be desirable to employ the material and methods disclosed in attempt to produce such molecules. However, the written description does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. It extends only to that which is disclosed. One shows that one is 'in possession' of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious.

Claims 29 and 36 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most clearly connected to make and/or use the invention, the Examiner stating:

> The claims are directed to "producing" a molecule. However, the specification does not describe the production of any and all molecules with the desired characteristics. In the absence of this information the skilled artisan would have to resort to a substantial amount of unduly extensive,

> random, trial and error experimentation in the form of random analysis of any and all compositions and/or compounds and through trial and error experimentation is left to determine how to isolate and produce them. In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

ISSUES

The following issues are presented in this Appeal.

1. Does claim 29 sufficiently definite to comply with 35 U.S.C. 112, second paragraph, despite the breadth of the "producing" step?

2. Does a screening process for finding molecules which cause the modulation of phosphorylation of a protein have a specific and substantial utility when the specification alleges a link between the phosphorylation and the biological activity of the protein?

3. Is a screening process claim supported by an adequate written description if the specification does not disclose any molecules which may be found by the claimed screening process?

4. Is it routine experimentation to screen for molecules which test positive in a screen and then to isolate and produce any such molecules?

GROUPING OF CLAIMS

For each rejection in which claims 29 and 36 were both rejected, the claims stand or fall together. The indefiniteness rejection applies only to claim 29.

A R G U M E N T

The Breadth of the "Producing" Step Does Not Render Claim 29 Indefinite

It is apparent that the Examiner has rejected the claim as being indefinite because of what the Examiner conceives to be the breadth of the claim. However, MPEP 2173.04 clearly sets forth the state of the law in this regard where it notes:

> Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.

Such is the case here.

The Examiner's use of the term "a process without any active, positive steps" is language very similar to that *Ex*

parte Erlich, 3 USPQ2d 101, 107 (Bd. Pat. App. & Int'f, 1987) rejecting a clam which reads, "A process for using monoclonal antibodies of claim 4 to isolate and purify human fibroblast interferon." In that case, the Board agreed with the appellants that the claims need not recite all of the operating details. But the Board ruled that a method claim should at least recite a positive, active step so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make it clear what subject matter these claims encompass, as well as making clear the subject matter from which others would be precluded. Here, claim 29 has two positive, active steps, a screening step and a producing step. These steps set forth what applicant claims to be their invention with a reasonable degree of precision and particularity. It is clear what subject matter these claims encompass and from which others would be precluded. One must first do a screening test, such as that set forth in step a). If any molecule is found in this screen, then it is produced as set forth in the producing step of step b). In the context of the present claim, the producing step is only one step of a two step process which defines novelty and reasonably sets forth the subject matter the claim encompasses. While the step b) is broad, this is not to be equated with indefiniteness. Reversal

of the Examiner and withdrawal of this rejection is therefore respectfully urged.

A Screening Process Based on Modulation of Phosphorylation is a Specific and Substantial Utility as the Specification Alleges a Link Between the Phosphorylation and the Biological Activity of the Protein

The present claims require that molecules be screened by testing each molecule to determine if the molecule causes modulation of the phosphorylation of the intracellular domain of the 26 kDa TNF by increasing or decreasing the extent of such phosphorylation. The Examiner states that the biological significance of this phosphorylation is unknown. However, this is incorrect. The present specification states at page 6, lines 3-10:

> Thus, the phosphorylation of the intracellular domain of the 26 kDa TNF molecules may be involved in the regulation of expression of proteolytic processing of cell-surface TNF, in the modulation of TNF bioactivity, or in the intracellular signaling process mediated by the cell-surface TNF molecule.
>
> The above findings and their related functional significance represent the first disclosure of a control possibility (both in terms of biological activity and amount) of the cell-surface form of TNF via control of the activity of the intracellular domain of this form of TNF, in particular, via control of the region in this domain which is subject to phosphorylation.

The specification, at page 12, lines 17-20, further states that the phosphorylation of the cell-bound TNF

constitutes part of the normal way of TNF modulation that "constitutes part of the normal way of TNF modulation." At page 13, lines 5-6, the specification states that the phosphorylation plays an important role in TNF function. Similarly, page 14, lines 1-7, states:

> Thus, in accordance with the present invention, the finding of phosphorylation of the intracellular domain of the cell-surface-bound form of TNF provides a basis for isolating agents on the one hand, and for pinpointing agents on the other, that can: (1) modulate the shedding (or proteolytic processing) of TNF, i.e. the release of the 17 kDa soluble form of TNF from the membrane-bound 26 kDa form; (ii) modulate the activity of TNF by intracellular signaling induced by the intracellular domain of TNF; or (iii) modulate the bioactivity of TNF via conformational interactions mediated by the intracellular domain.

Furthermore, at page 38, the present specification states that once molecules have been isolated which modulate the phosphorylation, those compounds can then be tested for their biological activity. Thus, at the very least the present specification discloses that the screening step of the present invention can be treated as a first step in a screening process to determine a class of molecules which may then be further screened *in vivo* for biological activity, which is also a specific and substantial utility.

It is thus clear that the specification makes specific assertions as to the utility of the invention in

indicating that the screening process is useful to find molecules that cause modulation of phosphorylation of the intracellular domain of the 26 kDa TNF in view of the further assertion that modulation of the phosphorylation would be expected to modulate the biological activity of the TNF. The specification establishes in the background section, such as at page 2, lines 8-29, that compounds which modulate TNF may be used for treatment of specific conditions, depending on whether they up-regulate or down-regulate TNF activity. Thus, there is a specific assertion in the specification that, regardless of whether phosphorylation is up-regulated or down-regulated, compounds found will have a specific and substantial use in treating specific disease conditions.

Reference is made MPEP 2107.01 III (August 2001 edition) which states:

> Similarly, courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition. The Federal Circuit, in *Cross v. Iizuka* 753 F.2d 1040, 1051, 224 USPQ 739, 747-8 (Fed. Cir. 1985), commented on the significance of data from *in vitro* testing that showed pharmacological activity:
>
> > We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for

> the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.

At the very least the screen of the present invention is the first link in the screening chain, *in vitro* testing. The successful screening test of the presently claimed invention will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds. This has been held to be a specific and substantial utility. Accordingly, reversal of the Examiner and withdrawal of this rejection is respectfully urged.

As the 35 U.S.C. 112, first paragraph, how to use rejection is based on the same reasons as the 35 U.S.C. 101 rejection, the Examiner should be overruled, and the rejection of claims 29 and 36 under 35 U.S.C. 112, first paragraph should also be withdrawn.

It is Not Necessary to Disclose Any Specific Molecules Which May be Found by a Claimed Screening Process in Order for an Applicant to be in Possession of the Process

It is important to note that neither claim 29 nor claim 36 requires that any molecule which cause modulation of the phosphorylation of the intracellular domain of the 26 kDa

TNF be actually identified. In this regard, the present case is similar to application no. 08/054,970, which is another case involving an invention from the laboratory of the present inventors, which has recently been decided by the Board of Patent Appeals and Interferences, Appeal No. 1999-0197. Attached hereto is a copy of the decision mailed November 21, 2001, which is particularly relevant to 35 U.S.C. 112 rejections of screening claims. While this decision has been indicated as not being binding precedent of the Board, it is believed that the reasoning found therein is relevant to the present case and should be adopted. In that case, the Board pointed out and explained to the Examiner that the claims did not require that any molecule actually be identified in the screen. Note where it states at page 8:

> By way of analogy, let us consider a claim directed to separating iron scrap from a waste stream by use of magnets. The fact that the waste streams processed according to that method may never contain iron scrap does not mean that the method is non-enabled.

The same logic obviously applies to whether applicant was in possession of the method. The producing step of claim 29 calls for "producing in substantially isolated and purified form any said molecule which is determined to cause said modulation." Thus, if no molecule is determined to cause the modulation then nothing need be produced. If any molecule is found that satisfies the requirements of the screening step,

then it is a trivial matter to produce it as is supported, for example at page 27, lines 5-11. Thus, applicants were in possession of the concept of producing a pure compound which has been identified, using synthesis processes already established in the art.

Applicants are not claiming molecules. Applicants are claiming a screen. The present specification specifically recites that the present invention relates to a screen. The method of the screen is clearly set forth in the specification. Thus, applicants are in possession of the concept of screening for molecules which have the desired characteristics. This is all that is necessary to satisfy the written description requirement of 35 U.S.C. 112. As the claim does not require that any such molecules be found, it is not necessary to identify any such molecule. However, once identified, the specification indicates that that molecule can be produced. Thus, applicants are also in possession of the idea of producing any molecule found. There is nothing in the first paragraph of 35 U.S.C. 112 which requires that such molecules be identified before one can be in possession of a screening process. Accordingly, reversal of the Examiner and withdrawal of this rejection is respectfully urged.

It is not Undue Experimentation to Screen for Molecules Which Test Positive in a Screen and Then to Isolate and Produce any Such Molecules

Reference is again made to the attached decision in application No. 08/054,970, which is directed to very similar types of claims. The Examiner states that the enablement requirement is not met because the specification does not describe the production of any and all molecules with the desired characteristics. However, the decision states at page 8:

> However, the examiner has lost sight of the fact that step [a)] of claim [29] only requires a screening step to identify any molecules which bind to the target peptide. Step [b)] only requires [production] if any molecules are identified in step [a)]. It may be that the material screened in screening step [a)] of claim [29] will not contain the specified molecules which bind to the target peptide. If so, then step [b)] would not be performed. That situation does not mean that claim [29] as whole is non-enabled. The examiner has not explained why the claimed screening methods would not identify the defined molecules if they are present in the material being screened.

The Board went on to state in the paragraph bridging pages 8 and 9:

> As we understand the examiner's position, it is premised in large part upon the fact that the specification of this application does not describe a specific molecule which possesses the binding requirements of the claims on appeal. However, the lack of

This passage has been amended to substitute reference to the corresponding portions of the present claims.

> description of a single specific molecule does not in and of itself mean that the claims are non-enabled. Rather, the specification need only teach one skilled in the art how to practice the claimed invention without undue experimentation. ….
>
> Absent a fact-based explanation from the examiner why the experimentation required to practice the methods set forth in the use claims on appeal would be undue rather than routine, we conclude that the Examiner has not established a prima facie case on enablement.

Here, the Examiner only states that the skilled artisan would have to resort to "a substantial amount of unduly extensive, random, trail and error experimentation in the form of random analysis of any all compositions and/or compounds and through trial and error experimentation". This is not so. The specification teaches exactly how to run the screen. A high throughput screen can determine binding of molecules to specified areas on the intracellular domain (see Example 6) and any molecules found tested for their effect of phosphorylation. This is not random trial and error, but a focused screen, using a disclosed assay to find and to identify the defined molecules if they are present in the material being screened. There is nothing random about it. The present claims are directed to a screening process and not to the molecules found. The Examiner's broad statement quoted above, which is merely conclusionary and without analytic backup, is no substitute for a fact-based

explanation why the experimentation required to practice the methods set forth in the present screening claims would be undue rather than routine. Thus, for the same reasons determined by the Board of Patent Appeals and Interferences in Appeal 1999-0197, the present enablement rejection must also be withdrawn.

Reversal of the Examiner and withdrawal of this rejection is therefore also respectfully urged.

CONCLUSION

The claims as submitted are believed to truly set forth the inventive concept of the present invention and to fully comply with the written description and enablement requirements of the first paragraph of 35 U.S.C. 112. Furthermore, a specific and substantial utility is disclosed in the specification so as to fully comply with 35 U.S.C. 101. The claims are not indefinite and fully comply with the second paragraph of 35 U.S.C. 112. Accordingly,

reversal of the Examiner and allowance of claims 29 and 36 are earnestly solicited.

Respectfully submitted,

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